Citation:

Ferrucci LM, Cross AJ, Graubard BI, Brinton LA, McCarty CA, Ziegler RG, Ma X, Mayne ST, Sinha R. Intake of meat, meat mutagens, and iron and the risk of breast cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Br J Cancer.* 2009 Jul 7; 101(1): 178-184.

PubMed ID: 19513076

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess meat intake and potentially carcinogenic meat-related exposures in relation to post-menopausal invasive breast cancer.

Inclusion Criteria:

Female participant of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Exclusion Criteria:

- Women who lacked the baseline questionnaire or the diet history questionnaire, had an incomplete diet questionnaire or were in the top or bottom 1% of energy intake for the cohort of women
- History of cancer other than non-melanoma skin cancer before dietary assessment
- No follow-up time.

Description of Study Protocol:

Recruitment

Participants were part of the PLCO Cancer Screening Trial, a multi-center, randomized controlled trial to evaluate screening methods for early detection of prostate, lung, colorectal and ovarian cancer. Recruitment occurred between 1993 and 2001.

Design

Prospective cohort.

Dietary Intake/Dietary Assessment Methodology

The Diet History Questionnaire: A self-administered, validated food-frequency questionnaire (FFQ).

Statistical Analysis

- Hazard ratios were estimated using Cox proportional hazards regression with age at baseline as the underlying time metric
- Tests for linear trend were based on median values of each quintile of dietary exposure
- Multivariate models adjusted for several potential confounders.

Data Collection Summary:

Timing of Measurements

- A self-administered baseline questionnaire was given at baseline
- The diet history questionnaire was administered once to each participant, starting in 1998
- Follow-up ended on December 31, 2006.

Dependent Variables

Invasive breast cancer: Incident cases were identified through self-report from annual study update questionnaire, physician reports or through reports from the next of kin, and were histologically confirmed based on pathology reports and medical records.

Independent Variables

- Intake of red meat (grams per day)
- Intake of white meat
- Intake of processed meat
- Intake of three heterocyclic amines (ng per day) and other meat mutagens
- intake of haem iron from meat.

Control Variables

Age, race, education, study center, randomization group, family history of breast cancer, age at menarche, age at menopause, age at first birth and number of live births, history of benign breast disease, number of mammograms in past three years, menopausal hormone therapy, body mass index and intakes of alcohol, total fat, and total energy.

Description of Actual Data Sample:

- *Initial N:* 154,952 (78,217 females)
- *Attrition (final N):* 52,158 females
- *Age:* 55 to 74 years at recruitment
- *Anthropometrics:* Post-menopausal (1.7% had ambiguous status)
- *Location:* United States.

Summary of Results:

Key Findings

- Comparing the first to the fifth quintile, there was a statistically significant positive associations between red meat and breast cancer (HR=1.23; 95% CI: 1.00 to 1.51, P=0.22), but no evidence of a dose-response effect
- There were no statistically significant associations of breast cancer with processed meat, white meat or individual meat items.

Other Findings

- Pan-fried meat, grilled meat, well or very well done meat, 2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine and benzo[a]pyrene were not associated with breast cancer
- Women in the highest quintile of 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline compared with those in lowest had statistically significant elevated risks of breast cancer (HR=1.26, 95% CI: 1.03 to 1.55, P=0.12)
- There was a marginally significant increased risk of breast cancer for women with the highest intakes of 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline and mutagenic activity; both associations had a statistically significant linear trend
- Dietary iron was positively associated with breast cancer in a dose-response manner (HR=1.25, 95% CI: 1.02 to 1.52, P=0.03), yet there was no association for total iron or iron from supplements.

Author Conclusion:

Red meat, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline and dietary iron elevated the risk of invasive post-menopausal breast cancer, but there was no linear trend in the association except for dietary iron.

Reviewer Comments:

Study Strengths

- *Investigated specific meat-related exposures*
- *Adjusted for total energy intake, and many other potential confounders in models.*

Study Limitations

- *Self-administered FFQ, which has measurement error*
- *Diet was assessed only once.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes

3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A

3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A

6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	???
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	N/A
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes

10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes